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Section III, Tox. Branch (TS-769C) 5/13/88

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rabbits

CHEMICAL: HOE 039866; Monoammonium [2-amino-4-(hydroxymethyl-phosphinyl)butanoate]; Ignite®

ACCESSION NUMBER: 403456-11 CASWELL NO.: 580I

EPA ID NO: 8340-EO/8340-EI EPA PROJECT NO: 8-0146

SPONSOR: Hoechst Celanese Corp.

TESTING FACILITY: Hoechst AG, 6230 Frankfurt am Main 80
Federal Republic of Germany

CITATION: Baeder, C., Kramer, M., et al. HOE 039866-- Active ingredient Technical; Testing for embryotoxicity in Himalayan Rabbits Following Oral Administration. Study No.: G2K0402; Project No.: 84.0177, April 9, 1984; Submitted by Hoechst Celanese Corp., Somerville, NJ.

CONCLUSION Groups of pregnant Himalayan rabbits (15/sex/dose) were administered HOE 039866 (technical) by gavage at doses of 2.0, 6.3, and 20.0 mg/kg from gestation days 7 to 19. Fetuses were delivered on day 29 by caesarean section. The following findings were reported:

1. Increased incidences of premature delivery, abortion, or early resorption and decreased body weight and food consumption in 20 mg/kg dams.

2. Decreased food consumption in 6.3 mg/kg dams.

3. Increased number of dead fetus/litter in 20 mg/kg group.

4. Increased incidence of weak or absent ossification of some skeletal bones in fetuses of 6.3 and 20 mg/kg groups.

5. Increased kidney weights of 20 mg/kg dams.

This report has several deficiencies which include (1) discrepancies in food consumption and in body weight data between summary data and individual animal data, (2) incomplete food consumption data for individual 20 mg/kg dams, and (3) vague diagnoses of the skeletal examination of the fetuses. These deficiencies do not allow accurate assessment of the developmental toxicity of the test agent on rabbits; therefore, NOEL and LEL are not established under the present conditions. The study is classified as Supplementary.

A. MATERIALS:

1. Test compound: Technical grade HOE 039866; Serial No. 12027; purity, 95.3%.

2. Test animals: 6-7 months old Himalayan rabbits, which weighed 2547±203 gm, were obtained from Hoechst breeding colony.

B. STUDY DESIGN:

Pairing

The females rabbits were paired with known fertile males. When sperm was detected in the vaginal smear, they were paired again 6 hours later. The day when pairing occurred was counted as day 0 of gravidity. Pregnancy status was confirmed by the presence of implantation sites in the uterus.

Compound Administration

The dosages were freshly prepared every day by dissolving the test chemical in distilled water at concentrations of 0.40, 1.26, or 4.00 gm/L. An equal volume of 5 ml/kg body weights was administered to each animal between 8 and 11 AM. The dosage for each animal was adjusted according to the current body weight. The prepared solution was found to be stable for 5 days. The female rabbits were dosed by gavage from day 7 to day 19 after coitus.

The female rabbits were randomly assigned to the following dose groups:

Test Group	Dose mg/kg	Number of rabbits Day 7-19 of gravidity
1 Cont.	0	15
2 Low (LDT)	2.0	15
3 Mid (MDT)	6.3	15
4 High(HDT)	20.0	16

The above dosages were chosen based upon the results of a range-finding study with 2 pregnant Himalayan rabbits/dose. The doses were 10.0, 22.4, and 50.0 mg/kg. At 22.4 mg/kg, body weight loss was observed in both dams. During the second week, one of the dams refused to eat, and it showed 3 dead fetuses and a conceptus under resorption in the uterus. At 50.0 mg/kg, the dams showed marked weight loss and clinical signs such as head tilting and twitching, forelegs twitching, and extension spasms. One dam was sacrificed on day 14 of pregnancy, and the other died on day 15.

Clinical examinations

Behavior and general health conditions of the animals were observed daily. Food intake was measured. The animals were weighed weekly during the first 3 weeks and then once more after a 9-day period.

Examinations following caesarean section

On day 29, all fetuses were delivered by caesarean section, and the dams were sacrificed. Uterus and placenta were weighed and examined; corpora lutea on the ovaries were counted and examined.

The fetuses were examined for outward appearance and overt anomalies. Subsequently, the body weights of these fetuses were determined, and they were kept for 24 hours in an incubator. The dead fetuses were noted, and the crown-rump length of the fetuses was measured. The sex of the fetuses was determined at autopsy.

Approximately half of the fetuses of each litter and all fetuses which had been born before term, aborted, or found dead in the uterus were fixed in alcohol, dissected, eviscerated, and bleached in aqueous potassium hydroxide. The skeletons were stained with Alizarin Red S and examined for developmental anomalies.

The remaining fetuses and 3 prematurely born fetuses were fixed in Bouin's fluid and examined in body cross-sections under a stereomicroscope for organ anomalies.

After fetuses were delivered, the dams were dissected, and organs were grossly examined. Heart, liver, kidneys, and spleen were weighed.

Statistical evaluation

The statistical methods are presented in Appendix 1.

RESULTS

Maternal Toxicity

1). Clinical examinations

Clinical observations are presented in Table 1.
In 20.0 mg/kg group, one dam showed "extension spasm" for approximately 5 sec on day 16. Subsequently, this animal remained in high-legged position with head stretched and tilted. In the following morning this dam was lying in its stomach in a state of apathy, and it was sacrificed. Another 20.0 mg/kg dam aborted on the night of day 19 of pregnancy, and a third dam delivered prematurely in the night of day 24.
In addition, a 6.3 mg/kg dam died on day 29 while given

premature birth, and this animal was included under the premature deliveries.

The 2.0 mg/kg females showed no abnormal behavior or ill health conditions. They all survived until the end of the study.

Increased incidences of reduced water consumption and defecation were also observed in treated dams relative to the controls.

2). Food consumption

Food consumption was decreased in all treated dams relative to the controls during the treatment period (days 7 to 19) (Table 2a). The reduced food intake was statistically significant for 6.3 and 20.0 mg/kg dams during the measuring interval of day 14-20. However, when the treatment stopped (day 20), the mean food consumption of 6.3 and 20.0 mg/kg dams was comparable to or even slightly greater than that of the controls.

There were some discrepancies concerning the food consumption data. For example, in the individual animal data, values for food consumption were reported for 7 animals in 20.0 mg/kg group for days 20-29 of pregnancy, and the mean was reported to be derived from these values. However, the summary data as presented in Table 1a indicated that the mean was derived from 6 dams and was different from the mean derived from the individual animals. Similar discrepancies also existed for 6.3 mg/kg dams.

3). Body Weight

There was a significant decrease in body weight of 20.0 mg/kg dams at days 20 and 29 measuring intervals (Table 2b). It should be noted that the summary data for 20.0 mg/kg dams as presented in Table 2b could not be verified by the individual animal data, and a similar discrepancy as that seen in food consumption data also existed in body weight data for this group and 6.3 mg/kg group.

FINDINGS FOLLOWING CAESAREAN SECTION

1). Table 3 presents the summary of the results at caesaren section. Most of the parameters examined were comparable between treated and control dams except the following:

a). decreased number of dams with live fetus in 20.0 mg/kg group.

b. decreased body weight gain in all treated dams during pregnancy and that of 20.0 mg/kg group was more marked and statistically significant ($p < 0.05$).

c. Increased number of dead fetuses/litter was observed in all treated groups, and that of 20.0 mg/kg group was reported to be greater than the normal range of the historical controls of the performing laboratory.

2. Skeletal and soft tissue examinations

a. The summary of skeletal "anomalies", "variations", and "retardation" is presented in Tables 4a, 4b, and 4c. There were increases in the incidence of "weak or absent ossification one or more head bones" and "weak or absent ossification of pubis, calcancus, talus" in the fetuses of mid and high dose groups (Table 4c). However, these finding could not be verified by the individual animal data. For example, the individual animal data often described the finding as weak or absent ossification of individual skeletal bones. If all those findings were combined, the sum did not match summary data as reported.

b. There was no difference in soft tissue findings between treated and control groups (Table 5)

3. Organ weights of the dams

There was a slight and statistically significant increase in kidney weights of the high dose dams (Table 6). Liver weights of all treated dams were increased relative to those of the controls, but this increase was not statistically significant and reported to be within the normal range of the findings for the performing laboratory.

DISCUSSION

Groups of pregnant Himalayan rabbits (15/sex/dose) were administered HOE 039866 (technical) by gavage at doses of 2.0, 6.3, and 20.0 mg/kg from gestation days 7 to 19. Fetuses were delivered on day 29 by caesarean section. The following findings were reported:

1. In 20 mg/kg dams, increased incidences of premature delivery, abortion, or early resorption, and significantly decreased body weight and food consumption were observed.

2. Significant decrease in food consumption was also observed in 6.3 mg/kg dams.

3. In 20 mg/kg group, the number of dams with live fetus/litter

was decreased, and accordingly the number of dead fetuses/ litter was increased.

4. Increased incidence of weak or absent ossification of some skeletal bones were reported in fetuses of 6.3 and 20 mg/kg groups. However, the accurate magnitude of this increase was difficult to determine because the individual animal data on skeletal examination contained rather vague diagnoses.

5. Slight but statistically significant increase in kidney weights of 20 mg/kg dams.

This report has several deficiencies which include (1) discrepancies in food consumption and in body weight data between summary data and individual animal data, and (2) vague diagnoses of the skeletal examination of the fetuses. These deficiencies do not allow accurate assessment of the developmental toxicity of the test agent on rabbits; therefore, NOEL and LEL can not be established under the present conditions. The study is classified as Supplementary.

TABLE 1

(DATA EXCERPTED FROM Submission)

Enclosure 1

Hoechst Aktiengesellschaft
Pharma Forschung Toxikologie

Survey of clinical findings in dams

Printed: 02/13/1986

Method: embryotoxicity — study no.: 02K0402

Preparation: Hoe 039866 01l ZC95 0001 vehicle: distilled water

Study	Start of Study	Animal	Route	Group/Sex/Dose
	09/05/1983	rabbit himalayan	oral	

caesarean section on day 29 — dosing from day 7 - 19 post copulation

Findings	Control	2.0 mg/kg	6.3 mg/kg	20,0 mg/kg
Number of dams	15	15	15	15
		Number of dams affected (% in brackets)		
Reduction of defecation	1 (6.7)	4 (26.7)	3 (20.0)	10 (66.7)
Reduction of fluid intake	1 (6.7)	3 (20.0)	3 (20.0)	9 (60.0)
Vaginal haemorrhage	0	0	0	1 (6.7)
Premature delivery	0	0	0	1 (6.7)
Dam died during premature delivery	0	0	1 (6.7)	0
Dam killed due to poor general health conditions	0	0	0	1 (6.7)

Continued Enclosure 2

TABLE 2a

DAILY FOOD CONSUMPTION G / 100 G BODY WEIGHT

DOSE MG/KG	DAY OF PREGNANCY 0 - 7 N	MEAN	SD		7 -14 N	MEAN	SD	14 -20 N	MEAN	SD		20 -29 N	MEAN	SD	
CONTROL	15	3.49	0.43	N	14	3.25	0.51	15	2.96	0.57	N	14	2.64	0.47	N
2.0	15	3.63	0.41	-N	12	2.50	0.39	11	2.64	1.34	-N	10	2.56	0.41	-N
6.3	13	3.48	0.67	-N	11	2.06	0.37	9	2.52	0.67	*N	8	2.53	0.43	-N
20.0	11	3.74	0.35	-N	7	1.28	0.85	8	1.82	1.22	*A	6	3.15	0.25	-N

THE FOOD CONSUMPTION IN G/100 G BODY WEIGHT WAS USED FOR THE EVALUATION. FOR DAYS 7-20 THE AREA UNDER THE CURVE.

EXPLANATION FOR EVALUATION SEE METHODS
- = NO DIFFERENCE FROM CONTROL (P>.05)
N = WITHIN THE NORMAL RANGE

* = SIGNIFICANTLY DIFFERENT FROM CONTROL (P<.05)
A = OUTSIDE THE NORMAL RANGE

TABLE 2b

BODY WEIGHT G

DOSE MG/KG	DAY OF PREGNANCY 0 N	MEAN	SD		7 N	MEAN	SD	14 N	MEAN	SD	20 N	MEAN	SD		29 N	MEAN	SD	
CONTROL	15	2559	181	N	15	2626	183	15	2676	185	15	2717	203	N	15	2087	189	N
2.0	15	2603	220	-N	15	2652	187	15	2655	166	15	2706	178	-N	15	2849	182	-N
6.3	14	2539	207	-N	14	2570	169	14	2571	162	14	2649	178	-N	14	2827	158	-N
20.0	11	2510	115	-N	11	2573	149	11	2468	152	11	2551	231	*N	11	2716	175	*N

THE AREA UNDER THE BODY WEIGHT CURVE WAS USED FOR THE EVALUATION OF DAYS 7-20.

EXPLANATION FOR EVALUATION SEE METHODS
- = NO DIFFERENCE FROM CONTROL (P>.05)
N = WITHIN THE NORMAL RANGE

* = SIGNIFICANTLY DIFFERENT FROM CONTROL (P<.05)
A = OUTSIDE THE NORMAL RANGE

(DATA EXCERPTED FROM Submission, TERATOLOGY study with HOE 039866 in Himalayan Rabbits)

TABLE 3

ENCLOSURE 2

HOECHST AG (DATA EXCERPTED FROM Submission) PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY PREPARATION: HOE 039866 OH ZC95 0001 ANIMAL: RABBIT HIMALAYAN
SEX: FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE: ORAL VEHICLE: DISTILLED WATER
START OF STUDY: 9/ 5/83 STUDY NO: G2K0402

SURVEY OF RESULTS AT CESAREAN SECTION

DOSE MG/KG			CONTROL		2.0		6.3		20.0	
EXPERIMENTAL FEMALES WITH SPERM / PREGNANT			15/15		15/15		15/15		16/15	
PREGNANT FEMALES - WHICH DIED OR WAS KILLED			0		0		0		1	
- WHICH DELIVERED PREMATURELY			0		0		1		1	
- WITH ABORTION OR ONLY EARLY RES			0		0		0		2	
FEMALES ON DAY 29										
- WITH IMPLANTATIONS			15		15		14		11	
- WITH DEAD IMPLANTATIONS ONLY			0		0		0		0	
- WITH LIVE FETUSES			15		15		14		11	
BODY WEIGHT GAIN G (DAY 0- 29)			327		245		287		206	+
MEAN NUMBER OF CORPORA LUTEA	+		7.9	N	8.3	-A	8.2	-A	8.2	-N
IMPLANTATIONS	+		7.3	N	7.1	-N	6.9	-N	7.1	-N
RESORPTION SITES	+		0.60	N	0.47	-N	0.36	-N	0.64	-N
DEAD FETUSES	+		0.00	N	0.20	-N	0.29	-N	0.55	-A
LIVE FETUSES	+		6.7	N	6.4	-N	6.2	-N	5.9	-N
RESULTS IN LIVE FETUSES :										
SEX, MALE/FEMALE %			46/54		57/43		51/49		43/57	
BODY WEIGHT G	+	MEAN	42.1	A	41.8	-(N)	42.7	-(N)	40.4	-(A)
		SD	5.1		3.0		4.3		6.6	
CROWN-RUMP LENGTH CM	+	MEAN	9.5	N	9.4	-N	9.6	-N	9.3	-N
		SD	0.4		0.4		0.3		0.6	
PLACENTAL WEIGHT G	+	MEAN	5.55	N	5.60	-N	5.76	-N	5.20	-N
		SD	1.04		0.70		0.72		0.74	
SURVIVAL RATE AFTER 24 HOURS %	+		93.6	N	88.1	-N	97.8	-N	90.3	-N

+ = STATISTICAL CALCULATION PERFORMED

EXPLANATION FOR EVALUATION AND (.) SEE METHODS
- = NO DIFFERENCE FROM CONTROL (P>.05) pg 0022 of SIGNIFICANTLY DIFFERENT FROM CONTROL (P<.05)
N = WITHIN THE NORMAL RANGE A = OUTSIDE THE NORMAL RANGE

STUDY A29082

+: statistically significant @ $P < 0.05$ with Two Sample T Test (Performed by the reviewer).

TABLE 4a

(DATA EXCERPTED FROM Submission)

ENCLOSURE 15
HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY
PREPARATION: Hoe 039866 OH ZC95 0001
CESAREAN SECTION ON DAY 29
DOSING FROM DAY 7 - 19 POST COPULATIONEM
ANIMAL: RABBIT HIMALAYAN

ROUTE: ORAL
VEHICLE: DISTILLED WATER
START OF STUDY: 09/05/1983
STUDY NO: G2K0402

SURVEY OF FINDINGS AT AUTOPSY AND SKELETON EXAMINATION

Dose mg/kg	control	2.0	6.3	20.0
	Number of foetuses affected/Number of litters affected (% in brackets)			
Number of foetuses examined/Number of litters:	53/15	54*/15	55**/14•	62***/11••
Anomalies				
Stomach taut with clear fluid and/or enlarged	-	1-/1- (2.0)/(6.7)	-	1-/1- (2.8)/(9.1)
Transverse position or caudad displacement of left kidney	-	1-/1- (2.0)/(6.7)	3-/2- (6.8)/(14.3)	-
Slight splitting of os parietale at sagittal suture	-	-	-	1-/1- (2.8)/(9.1)
Slight splitting of os parietale in region of fontanelle on right side	-	-	1-/1- (2.3)/(7.1)	-
Dorsal fragmentation of right arch of 2nd cervical vertebra	-	1-/1- (2.0)/(6.7)	-	-

of these, * 3, ** 11, *** 26 stunted, prematurely delivered, aborted or retarded dead foetuses, not included in percentage calculation

of these • 1, •• 3 litters not included in percentage calculation due to premature delivery, abortion or premature sacrifice

x = aborted, prematurely delivered or retarded dead foetuses

Continued Enclosure 16

TABLE 46

(DATA EXCERPTED FROM Submission)

ENCLOSURE 16
HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY
PREPARATION: Hoe 039866 OII ZC95 0001
ANIMAL: RABBIT HIMALAYAN
CESAREAN SECTION ON DAY 29
DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE: ORAL
VEHICLE: DISTILLED WATER
START OF STUDY: 09/05/1983
STUDY NO: G2K0402

SURVEY OF FINDINGS AT AUTOPSY AND SKELETON EXAMINATION

Dose mg/kg	control	2.0	6.3	20.0
	Number of foetuses affected/Number of litters affected (% in brackets)			
Number of foetuses examined/Number of litters:	53/15	54*/15	55**/14•	62***/11••
Anomalies				
Fused, dysplastic, dislocated sternebrae	4/3 (7.6)/(20.0)	3-/3- (5.9)/(20.0)	1-/1- (2.3)/(7.1)	1-/1- (2.8)/(9.1)
Fused caudal vertebrae	-	1-/1- (2.0)/(6.7)	-	-
Variations				
Primordium of a short rib on 7th cervical vertebra, unilaterally or bilaterally	2/2 (3.8)/(13.3)	-	5-/3- (11.4)/(21.4)	-
Primordium of a short and/or normal length 13th rib, unilaterally or bilaterally	3/3 (5.7)/(20.0)	2-/2- (3.9)/(13.3)	3-/3- (6.8)/(21.4)	4-/3- (11.1)/(27.3)

of these, * 3, ** 11, *** 26 stunted, prematurely delivered, aborted or retarded dead foetuses, not included in percentage calculation

of these • 1, •• 3 litters not included in percentage calculation due to premature delivery, abortion or premature sacrifice

Continued Enclosure 17

TABLE 4c

(DATA EXCERPTED FROM Submission)

ENCLOSURE 17
HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY — PREPARATION: Hoe 039866 OH ZC95 0001 — ANIMAL: RABBIT HIMALAYAN
CESAREAN SECTION ON DAY 29 — DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE: ORAL — VEHICLE: DISTILLED WATER
START OF STUDY: 09/05/1983 — STUDY NO: G2K0402

SURVEY OF FINDINGS AT AUTOPSY AND SKELETON EXAMINATION

Dose mg/kg	control	2.0	6.3	20.0
	Number of foetuses affected/Number of litters affected (% in brackets)			
Number of foetuses examined/Number of litters:	53/15	54*/15	55**/14•	62***/11••
Retardations				
Weak or absent ossification of one or more head bones	-	-	$3^{x}/2$	$9^{x}/4$
Weak or absent ossification of os pubis, calcaneus, talus	-	-	$2^{x}/2$	$9^{x}/4$
Non-ossification of one or more sternebrae	22/10 (41.5)/(66.7)	22/11- (43.1)/(73.3)	23-/12- (52.3)/(92.3) $4^{x}/2$	16-/8- (44.4)/(100.0) $4^{x}/2$

of these, * 3, ** 11, *** 26 stunted, prematurely delivered, aborted or retarded dead foetuses, not included in percentage calculation

of these • 1, •• 3 litters not included in percentage calculation due to premature delivery, abortion or premature sacrifice

^{x} = aborted, prematurely delivered or retarded dead foetuses

Continued Enclosure 18

TABLE 5

(DATA EXCERPTED FROM Submission)

ENCLOSURE 18
HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY — PREPARATION: Hoe 039866 OH ZC95 0001 — ANIMAL: RABBIT HIMALAYAN
CESAREAN SECTION ON DAY 29 — DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE: ORAL — VEHICLE: DISTILLED WATER
START OF STUDY: 09/05/1983 — STUDY NO: G2K0402

SURVEY OF FINDINGS AT SOFT TISSUE EXAMINATION

Dose mg/kg	control	2.0	6.3	20.0
	Number of foetuses affected/Number of litters affected (% in brackets)			
Number of foetuses examined/Number of litters:	48/15	45/15	43*/14•	29/11••
Anomalies				
Stomach in transverse position, or taut with clear fluid and/or enlarged	2/2 (4.2)/(13.3)	2-/2- (4.4)/(13.3)	2x/1	1-/1- (3.5)/(9.1)
Dilation of renal pelvis, bilaterally	-	-	-	1-/1- (3.5)/(9.1)
Caudad displacement and/or transverse position of left kidney	3/3 (6.3)/(20.0)	1-/1- (2.2)/(6.7)	4-/4- (10.0)/(28.6)	3-/3- (10.3)/(27.3)

of these, * 3 stunted, prematurely delivered, aborted or retarded dead foetuses, not included in percentage calculation
of these • 1, •• 3 litters not included in percentage calculation due to premature delivery, abortion or premature sacrifice
x = aborted, prematurely delivered or retarded dead foetuses

TABLE 6

HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY: EMBRYOTOXICITY PREPARATION: HOE 039866 OH ZC95 0001 ANIMAL: RABBIT HIMALAYAN
SEX: FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE: ORAL VEHICLE: DISTILLED WATER
START OF STUDY: 9/ 5/83 STUDY NO: G2K0402

SURVEY OF BODY AND ORGAN WEIGHTS G IN DAMS

DOSE MG/KG	BODY WEIGHT N	MEAN	SD	HEART N	MEAN	SD		LIVER N	MEAN	SD		KIDNEYS N	MEAN	SD		SPLEEN N	MEAN	SD	
CONTROL	15	2887	189	15	5.16	0.64	N	15	57.03	7.57	N	15	15.06	1.45	N	15	0.64	0.14	N
2.0	15	2849	182	15	5.36	0.44	-N	15	59.65	7.50	-N	15	15.31	1.72	-N	15	0.68	0.10	-N
6.3	14	2827	158	14	5.33	0.63	-N	14	61.96	5.62	-N	14	15.85	1.33	-A	14	0.67	0.12	-N
20	11	2716	175	11	5.16	0.79	-A	11	63.48	6.55	-N	11	16.65	1.70	*A	11	0.60	0.14	-N

EXPLANATION FOR EVALUATION SEE METHODS
- = NO DIFFERENCE FROM CONTROL (P>.05)
N = WITHIN THE NORMAL RANGE

* = SIGNIFICANTLY DIFFERENT FROM CONTROL (P<.05) (verified by this Reviewer).
A OUTSIDE THE NORMAL RANGE

(DATA EXCERPTED FROM Submission)